Risk of Urinary Bladder Tumours in Firemen

STUDIES AND RESEARCH PROJECTS

Douglas B. McGregor

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REPORT

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March 2005.

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This study was financed by the IRSST. The conclusions and recommendations are those of the author.

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Urinary Bladder Tumours

Cancers of the urinary bladder account for approximately two-thirds of all urinary tract cancers and are the ninth most common cancer worldwide, the annual incidence of new cases being about 330,000 and the number of deaths from the disease being in excess of 130,000. In northern America there are about 48,000 new male cases annually (including almost 4000 in Canada). It primarily occurs among older, white men. In Canada, the male-to-female ratio for the incidence of bladder cancer is approximately 3:1 and approximately 70% of the cases are diagnosed after the age of 65 years (Ferlay et al., 2001). The age-standardised incidence rate (world comparison) for the period 1988 – 1992 was 24.05 for white males and 11.10 for black males in the USA (Parkin et al., 1997). More than 90% of the histologically diagnosed urinary bladder cancers are transitional cell carcinomas; other types are consequently uncommon and include adenocarcinomas (6%), squamous cell carcinomas (2%) and small cell carcinomas (<1%). Transformation of bladder transitional epithelial cells can give rise to a carcinoma *in situ*, which can take several clinical forms, one of which involves invasion of the submucosa and muscularis (25% of the cases). The majority (70%), however, do not invade the muscularis propria and adopt a papillary form.

The most important risk factor for urinary bladder cancer is cigarette smoking, which accounts for approximately 65% of male and 30% of female cases (Brennan et al., 2000). It seems that air-cured (black) tobacco confers a greater risk than flue-cured (blond) tobacco. There was a linear increasing risk of bladder cancer with increasing duration of smoking, ranging from an odds ratio (OR) of 1.96 after 20 years of smoking (95% confidence interval [CI] 1.48-2.61) to 5.57 after 60 years (CI 4.18-7.44). A dose relationship was observed between number of cigarettes smoked per day and bladder cancer up to a threshold limit of 15-20 cigarettes per day, OR = 4.50 (CI 3.81-5. 33), after which no increased risk was observed. An immediate decrease in risk of bladder cancer was observed for those who gave up smoking. This decrease

was over 30% after 1-4 years and was over 60% after 25 years of cessation. However, even after 25 years, the decrease in risk did not reach the level of the never-smokers. It has been postulated that the bladder carcinogenic activity of tobacco smoke is due to the aromatic amines it contains, such as benzidine, 4-aminobiphenol, 2-naphthylamine and 4-chloro-*o*-toluidine. Involuntary smoking of tobacco has not been associated with cancer of the urinary bladder (IARC, 2004). Another non-occupational exposure that is a risk for urinary bladder cancer is the use of analgesics containing phenacetin (classified by IARC as human carcinogens, *Group 1*, IARC, 1987). Phenacetin was produced in northern America from the 1930's, but its use was withdrawn in Canada in 1978 (WHO, 1978). Case-control studies have been consistent in showing a positive association between cancer of the renal pelvis and cancer of the urinary bladder and use of phenacetin-containing analgesics, with relative risks varying from 2.4 to over 6; these associations have not been explained by confounding with other causes of urothelial cancer, and, where looked for, a positive dose-response relationship has been evident (McCredie et al., 1982, 1983, McLaughlin et al., 1984, Piper et al., 1985, 1986). Drinking coffee has also received an IARC carcinogenicity classification for urinary bladder, but the evidence is not convincing (*Group 2B*, IARC, 1991). Although not an issue in Canada, the urinary bladder is susceptible to neoplasia as a result of infection with the trematode, *Schistosoma haematobium*, (classified by IARC as a human carcinogen, *Group 1*, IARC, 1994). The interest of this agent is that, although other infections and infestations of the urinary bladder have not received the same attention, there is mixed evidence that they may also constitute risks. Thus, Kantor et al. (1984) found an increased risk associated with urinary tract infections in both men and women in the U.S.A.; subjects with a history of at least three infections had a relative risk of 2.0, compared with those reporting no infections. It is noted, however, that the association is stronger for squamous cell carcinoma, as is the case for *S. haematobium*.

Occupational exposure to aromatic amines, such as benzidine and 2-naphthylamine, has also been associated with high risk (Silverman et al., 1996). Occupations in which increased risk of urinary bladder cancer have been reported include dyestuffs manufacture and use, aromatic amine manufacture, painting, driving motor vehicles and working in the rubber, leather or aluminium industries (reviewed by Silverman et al., 1996). In some of these occupations there is clearly opportunity for exposure to aromatic amines, but exposure to polycyclic aromatic hydrocarbons (PAH) also occurs. The possible impact of PAHs on cancer incidence and mortality in various industries has been reviewed (Boffetta et al., 1997). The industries covered were aluminium production, coal gasification, coke production, iron and steel foundries, tar distillation, shale oil extraction, wood impregnation, roofing, road-paving, carbon black production, carbon electrode production, chimney sweeping and calcium carbide production. In addition, evaluation was made of workers exposed to diesel engine exhausts. Heavy exposure to PAHs from coal tars and pitches entails a substantial risk of urinary bladder cancer that is not likely to be due to other carcinogenic exposures present in the same industries. However, a population-based case-control study of the effect of exposure to either benzo(*a*)pyrene specifically or to PAHs in general from a large number of occupational and environmental exposures in Montréal provided no evidence of a PAH effect among either non-smokers or smokers (Nadon et al., 1995). Fifteen additional case-control studies of bladder cancer and exposure to PAHs were reviewed by Boffetta et al. (1997), who concluded that they tended to report positive results for exposure to PAHs, although statistical

significance was reached for only two of the 32 odds ratios presented, possibly due to the small number of cases in the different exposure categories. It had been suggested previously that aromatic amines (particularly 2-naphthylamine) might be responsible for the bladder cancer observed in some of these industries (Armstrong et al., 1986). In the two studies, however, that addressed PAH exposure from any occupational source (Bonassi et al., 1989; Clavel et al., 1994), after controlling for exposure to aromatic amines, increased risks for urinary bladder cancer were found in the highest exposure category.

Firemen: General Characteristics and Exposures

Fighting fires is a mentally and physically demanding occupation in which burns, falls and crush injuries are commonplace and exposure to smoke and other airborne organic and inorganic substances is taken for granted (Gochfeld, 1995). The largest category of non-fatal fire fighter injuries associated with fires has been reported to be contact with flames and smoke (39%) and the leading cause of non-fatal injury among younger firemen is related to smoke inhalation (FEMA, 1990). Approximately 90% of structural fires are either extinguished or abandoned and fought from outside within 5 – 10 min., the average duration of heavy physical activity being 10 min. (Gilman & Davis, 1993).

The task of fire fighting consists of two phases: (1) *knockdown*, during which the fire is brought under control, and (2) *overhaul*, when the fire is extinguished and clean up begins. Although self-contained breathing apparatus (SCBA)s are available, these are seldom worn from the time the firemen arrive at the scene until the time that they leave. In a study of exposures in the City of Montréal fire department, Austin et al., 2001a, found that SCBAs were worn about 50% of the time at structural fires, but they were worn for only 6% of the total time spent at all types of fires. Masks are generally put on when the firemen enter a fire or "see smoke," but it is difficult for them to judge when the mask can be safely removed and they are rarely worn during the smouldering phase of a fire or during mop-up operations. Furthermore, communication is essential and this is difficult with the mask in place.

It is recognised that during overhaul, recommended ceiling or short-term exposure levels can often be exceeded, e.g., for acrolein, benzene, carbon monoxide, formaldehyde, glutaraldehyde, nitrogen dioxide and sulphur dioxide (Bolstad-Johnson et al., 2000). Several toxic materials, e.g., carbon monoxide and benzene, were found to be present at appreciable concentrations in the atmosphere at real fire scenes when SCBAs were only used part of the time or not at all, owing to the impression that there was low smoke intensity (Brandt-Rauf et al., 1988, 1989). In a study of municipal structural fires, Austin et al., 2001b found that the spectra of volatile organic compounds were similar and remarkable for their simplicity, being dominated by benzene along with toluene and naphthalene. They also found that propylene and 1,3-butadiene were present in all of the fires and that styrene and other alkylated benzenes were frequently identified. Indeed, just 14 different compounds accounted for about 75% of the total volatile organic materials measured, these being: propene, benzene, xylenes, 1-butene/2-methylpropene, toluene, propane, 1,2-butadiene, 2-methylbutane, ethylbenzene, naphthalene, styrene, cyclopentene, 1-methylcyclopentene and isopropylbenzene. These same compounds constituted approximately 65% of all volatile organic compounds in experimental fires burning

various materials commonly found in structural fires (Austin et al., 2001c). None of these compounds has been implicated as human urinary bladder. Other materials that have been quantified with some regularity include acrolein, carbon monoxide, formaldehyde, glutaraldehyde, hydrogen chloride, hydrogen cyanide and nitrogen dioxide (Bolstad-Johnson et al., 2000; Caux et al., 2002). There may also be exposure to asbestos and various metals, such as cadmium, chromium and lead. In addition, there is almost certainly exposure to diesel exhaust and fumes and to PAHs.

Studies Reviewed.

A recent review of latent health effects, particularly cancers, in firemen (Haas et al., 2003) included many of the publications considered below. Some of the publications included here in the assessment of effects on urinary bladder cancer were dismissed by Haas et al. (2003) on the grounds that proportionate mortality ratios were used in the analysis (Feuer & Rosenman, 1986; Burnett et al., 1994; Grimes et al., 1991); they did not contain duration of employment data (Hansen, 1990, Baris et al., 2000; Deschamps et al., 1995); or they were over-lapping studies (Heyer et al., 1990 overlapping with Demers et al., 1992). The conclusion of Haas et al. (2003) was that there was no convincing evidence that employment as a fireman is associated with all-cause, coronary artery disease, cancer or respiratory disease mortality. This review unfortunately omitted the Baris et al. (2001) paper, a particularly informative publication, from consideration. Because of the heterogeneity of the studies, it was considered inappropriate to attempt any overall quantitative assessment, so this review is confined to a qualitative evaluation of the available evidence.

There have been many studies of mortality amongst firemen, but only a few have specifically identified urinary bladder as a possible target for carcinogenesis. These (eight) studies are reviewed here, independently of the opinions expressed by Haas et al. (2003).

The mortality experience was studied of 1867 white male firemen employed by the City of Buffalo for a minimum of five years with at least one year as a fireman between January 1950 and October 1979 (Vena & Fiedler, 1987). At the end of this period, the vita status of 99% of the firemen was determined, resulting in 470 observed deaths. Death certificates were obtained for 94% of the observed deaths. There were 32858 person-years available for analysis. Person-years combined into five-year age-time categories and multiplied by the corresponding age-time specific USA mortality rates for white men yielded the expected number of deaths. Deaths from cancer, all causes, was not different from the expected, the Standardised Mortality Ration (SMR) being 1.09 with 95% Confidence Intervals (CI) of 0.89-1.32. For urinary bladder cancer, however, there was a significant increase in mortality, with the SMR = 2.86 (CI 1.30-5.40) based on 9 deaths. All of these men had been employed before 1930 and the latency was at least 30 years (one death, 0.9 expected). The maximum number of urinary bladder deaths (five) occurred with latencies of 40-49 years when expected rate was 1.1. The remaining three deaths occurred with latencies > 50 years, when 0.5 were expected.

Case-control analyses were conducted in a surveillance study in Massachusetts to examine associations between fire fighting and cancer incidence, urinary balder cancer being one of nine that were studied (Sama et al. 1990). Subjects were

identified through the state cancer registry files for 1982-86. Two "unexposed" reference populations were used: policemen and males state wide. Standardised morbidity odds ratios (SMOR) were statistically significantly increased for urinary bladder cancer among firemen compared with both the state-wide male referents, SMORm = 1.59 (CI 1.02-2.50) and police referents, SMORp = 2.11 (CI 1.07-4.14).

Mortality rates were calculated for 3066 firemen who had been employed in San Francisco, CA between 1940 and 1970 (Beaumont et al., 1991). Vital status was ascertained until 1982 and Rate Ratios calculated using USA death rates for comparison. Amongst 1186 deaths there were 236 cancer deaths, approximately as expected, RR = 0.95 (0.84-1.08). For bladder cancer, the rate ratio was lower than expected, but not significantly so, RR = 0.57 (0.19-1.35) based on 5 deaths.

The mortality of 4546 men employed as firemen in Seattle and Tacoma, WA, and Portland, OR, USA for at least one year between 1944 and 1979 was compared with the national mortality in the USA (m) and with police mortalities (p) in the same cities (Demers et al., 1992). Between 1945 and 1989 there were 1169 deaths in the study population, 291 being cancer deaths. There was no excess risk of overall cancer mortality: IDRp = 0.97 (0.67-1.33), SMRm = 0.91 (0.85-1.07) or urinary bladder cancer in particular: IDRp = 0.16 (0.02-1.24), SMRm = 0.23 (0.03-0.83). This study, like most others on firemen, relied upon death certificates for cause of death information.

A later study of cancer in firemen by the same group reduced the study size to Seattle and Tacoma, WA, USA, which allowed them to use tumour registry data, rather than death certificates, for 2447 firemen (Demers et al., 1994). Duration of active duty was assignable for Seattle firemen and used as a surrogate measure of cumulative exposure to combustion products from fires; no exposure was assigned for years spent in administrative duties or support services. Total years of employment had to be used for Tacoma firemen because records identifying the start and end dates of specific duties were not available for all of them. The study population was followed for 16 years (1974-89) and the cancer incidence compared with that in 1878 policemen from the same cities. There were 244 cancer deaths in the study population. There was no excess risk of overall cancer mortality: SIRp = 1.0 (0.8-1.3), SIRm = 1.1 (0.9-1.2) nor was there a statistically significant excess risk of urinary bladder cancer in particular: SIRp = 1.7 (0.7-4.3), SIRm = 1.2 (0.7-1.9). SIRs were also calculated according to duration of exposed employment, but this did not reveal any underlying relationship of risk with increasing surrogate for exposure.

A historical cohort was assembled of all firemen employed between 1927 and 1987 in Edmonton and Calgary, Alberta (Guidotti, 1993). Even short employment periods (< 1 year) were justified on the grounds that much of the first year is in training with considerable exposure to smoke and the use of breathing apparatus. An exposure opportunity index term, reflecting estimates of the relative time spent in close proximity to fires by job classification, was applied to refine exposure data based on years of service. The applied weightings were: fireman lieutenant and captain = 1.0; safety or training officer = 0.2; district chief or volunteer fireman = 0.1; desk job and other posts not involving active fire fighting = 0.0. The firemen were followed for 64983 person-years and the vital status determined for 3193, which included 370 deaths, 92 being due to cancer. This provided a significantly increased risk for all

cancers, standardised mortality ratio (SMR) = 1.14 (1.02-1.55)[1] based on the 92 cases. For cancers of the urinary bladder, SMR = 3.16 (0.86-8.08) based on 4 cases. Three of the four cases were seen in men entering the fire service before 1920, the remaining one having joined in the 1940s. The earliest case appeared at least 30 years after entry, the maximum risk occurring 40-49 years after entry.

A cohort study of 5414 firemen in metropolitan Toronto, Ontario was conducted on all employees who had worked for at least 6 months at any time between 1950 and 1989 (Aronson et al., 1994). Deaths and causes of deaths were obtained by computerised record linkage. There were 114008 person-years of follow-up. The average years of follow-up and years of employment were 21 and 20, respectively. The incidence of all cancers combined was not elevated, SMR = 1.05 (0.91-1.20) based on 199 cases. The SMR for urinary bladder cancers was 1.28 (0.51-2.63) based on 7 cases. Portions of the data were also analysed after stratification according to years since first exposure and years of employment, but the urinary bladder cancer data were too meagre for this analysis to be performed.

A particularly large investigation made into the occurrence of cancer death in firemen was that of Burnett et al., 1994, which unfortunately was reported only as a brief communication (although full details are available from the authors). This was a proportionate mortality study of white firemen in 27 states of the USA from 1984 through 1990, using data from the National Occupational Mortality Surveillance system. There were 5744 deaths, 1636 being due to cancer. The proportionate mortality ratio (PMR) was statistically significantly increased for all cancers combined, PMR = 1.10 (1.06-1.14) and for that portion of the cases who died at < 65 years of age, PMR = 1.12 (1.04-1.21). For all urinary bladder cancer deaths the PMR = 0.99 (0.70-1.38) based on 37 deaths and for those that died at age <65 years, the PMR = 1.01 (0.46-1.93) based on 9 cases. The small number of deaths occurring below the age of 65 underlines the common observation that cancer of the urinary bladder mainly a disease of old age. The strength of this study is its very large numbers of cancer deaths. Its weaknesses (shared by other studies of this type) were listed by the authors and, because they apply to any study of this type, are listed in the Discussion section.

A related study was that of Ma et al., 1998, who used a database overlapping that of Burnett et al., 1994, but their stated objective was to examine possible racial differences in susceptibility to cancer mortality. Furthermore, although the database was extended by three years to 1993, some data were lost because three states were removed from consideration (Alaska, New York and Pennsylvania). There were 6607 deaths, 1817 being due to cancer. Although the stated objective was a racial comparison, there were only 66 cancer deaths amongst blacks, while there were 1817 amongst whites. For all cancers combined amongst whites, the mortality odds ratio (MOR) = 1.1 (1.1-1.2) based on 1817 deaths, while amongst blacks the MOR = 1.2 (0.9-1.5) based on 66 deaths. For urinary bladder cancer deaths amongst whites, the MOR = 1.2 (0.9-..6) based on 48 deaths, while there was just one case of urinary bladder cancer was recorded amongst blacks. The likely large degree of overlap with the Burnett et al., 1994 study indicates that these cannot be considered as completely independent investigations of urinary bladder cancer.

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[1] risk ratio (95% confidence interval)

Bates et al., 2001 made a historical cohort study of all paid firemen in New Zealand from 1977 to 1995. The data were obtained from a registry of all firemen maintained by the United Fire Brigades Association of New Zealand (UFBA), principally for confirming eligibility for long-service awards. The study cohort was defined as every person in the UFBA database who had worked as a fireman for at least one year and who had been paid for at least one day in the study period. Anonymous cancer and mortality data came from the New Zealand Health Information Service. General population data, by age and sex, was obtained for 5-year periods of the census years between 1971 and 1996. The final cohort contained 4305 firemen (4221 male, 84 female). The cancer follow-up time for the cohort was 62366 male person-years and 691 female person-years. The standardised incidence ratio (SIR) for all male cancers combined was not elevated, SIR = 0.95 (0.8-1.1) based on 118 cases. The incidence of male cancer of the urinary bladder was 1.14 (0.4-2.7) based on five cases.

From the point of view of measures of exposure, length of the historical cohort and the length of follow-up, the study of firemen in Philadelphia, 1925 to 1986, conducted by Baris et al., 2001, is particularly valuable. Comparison was made against the general white male population of the USA. The 7789 firemen were normally employed in their late 20s and worked for an average of 18 years, with an average of 26 years follow-up. This provided 204821 person-years of follow-up in which there were 2220 deaths, of which 500 were due to cancer. Thus, this study involved a cancer study population of about 30% the size of Burnett et al., 1994 or Ma et al., 1998. The measures of exposure that were used were:

1. duration of employment (≤ 9 years; 10 – 19 years; ≥ 20 years);
2. type of company employment (engine only; ladder only; engine and ladder);
3. year of hiring (before 1935; 1935-1944; after 1944);
4. cumulative number of fire runs (low, ≤ 3323; medium, ≥ 3323 & ≤ 5099; high, > 5099, i.e., less than the median, $\geq$ median and $\leq 75^{th}$ percentile, and $\geq 75^{th}$ percentile);
5. accumulation of fire runs (low, ≤ 3191; high, > 3191);
6. fire runs during first 5 years as a fireman (low, ≤ 729; high, > 729), and
7. lifetime fire runs with diesel exposure (non-exposed; low exposed, 1 – 259 runs; medium exposed, 260 – 1423 runs; high, ≥ 1423 runs).

The overall risk of mortality from urinary bladder cancer was not significantly increased among firemen, with SMR = 1.25 (0.77-2.00) based on 17 deaths and showed no relationship with duration of employment, the highest SMR being for the sub-group employed for 10-19 years, SMR = 1.48 (0.70-3.09) based on 7 deaths. Year of first employment before 1935 showed the strongest indication of an association with the risk of urinary bladder cancer, SMR = 1.71 (0.94-3.08) based on 11 of the 17 deaths. There was, however, no increased risk associated with ≥ 20 years employment, SMR = 1.01 (0.45-2.25) based on 6 deaths. The risk of urinary bladder cancer was not increased in firemen who worked only in engine crews, SMR = 0.53 (0.17-1.65) based on 3 deaths and although the risk was higher in ladder crews, SMR = 1.81 (0.45-7.23) this assessment was based on just 2 deaths and was not statistically significant. Analysis of data for exposure described by the cumulative number of fire runs in any position (fireman, lieutenant or captain), be these designated as low, medium or high, was based on numbers that were too small meaningful results for

urinary bladder cancer. In contrast, there was an increased risk of urinary bladder cancer mortality associated with high numbers (> 729) of fire runs during the first 5 years of employment, RR = 2.59 (0.46-14.59) based on 4 out of 6 deaths.

Studies Reviewed but not Considered in the Evaluation

In addition to the studies listed in Table 1 and described above, there were 3 groups of publications on cancer epidemiology of firemen that were examined. Of these,

1. Five studies have listed cancers that might include those of the urinary bladder under the headings of either genitourinary or urinary tract cancers (Musk et al., 1978; Eliopulos et al., 1984; Grimes et al., 1991; Giles et al., 1993; Deschamps et al., 1995). Of these, a significantly increased risk of genitourinary cancers was recorded in a cohort of firemen in Honolulu, Hawaii: proportionate mortality ratio, 2.28 (1.28-4.06) (Grimes et al., 1991) and an elevated, but not statistically significant increase was recorded in another cohort in Paris, France: standardised mortality ratio, 3.29 (0.40-11.88), this result being based on just two cases (Deschamps et al., 1995). The three remaining studies showed no remarkable risks for genitourinary cancer: these being a study in Western Australia: SPMR, 1.08 (0.29-2.76) (Eliopulos et al., 1984), a study in Victoria, Australia: standardised incidence ratio: 1.02 (0.28-2.62) (Giles et al., 1993) and a study in Boston, Massachusetts, with a total of 367 cancer deaths, in which there was a standardised mortality ratio of 0.92 for genitourinary cancers combined (Musk et al., 1978).

2. The following publications did not report urinary bladder cancer (or the incidence of urinary bladder cancer was zero):
Mastromatteo, 1959, with 34 cancer deaths;
Williams et al., 1977, with 58% interviews of 13179 cancer cases in 8 regions of USA;
Feuer & Rosenman, 1986, with 23 cancer deaths;
Hansen, 1990, with 21 cancer deaths;
Heyer et al., 1990, with 92 cancer deaths;
Tornling et al., 1994, with a cancer incidence of 127;
Lee et al., 1996, with 1439 cancer deaths in 24 states of the USA;
Ide, 1998, with 8 malignancies diagnosed.

3. They were case-control studies on firemen, but examining cancers other than those of the urinary bladder (Morton & Marjanovic, 1984; Demers et al., 1993; Bates & Lane, 1995; Delahunt et al., 1995; Figgs et al., 1995; Finkelstein, 1995)

Discussion

1. Problems in assessment.

a. Healthy worker effect.

Firemen tend to have a lower mortality rate than the general population, at least during the earlier years of employment. It may be that front line firemen are a work population particularly prone to a healthy worker effect, since it appears that many firemen who develop symptoms early in their careers may be moved to other, non-fire-fighting roles (Guidotti & Clough, 1992). This suggestion is supported by the higher prevalence of non-specific respiratory disease amongst firemen who do not

actually fight fires (Peters et al., 1974). According Guidotti, 1995, the healthy worker effect seems to be important during the first 20 years or so of employment, due in large part to a reduction in cardiovascular disease, but tends to disappear with longer employment. Bias of this kind, should it occur, is more likely to affect disease categories other than cancer. In the study of Baris et al., 2001, the SMR for all causes of death was significantly reduced during the first 9 years and after 20 years of employment, but not in the employment range 10 – 19 years. These changes seemed to be largely due to changes in SMRs for circulatory disease and ischaemic heart disease. Guidotti, 1995, has suggested that the healthy worker effect late in employment could be due to the removal of workers (because they become unfit) from exposure to risk factors predisposing them to early mortality.

b. Inter-study comparison of exposure

In reviewing the literature covering studies of firemen in different parts of the world, with the intention of applying the results to a particular region, it is as well to be aware that the definition of exposure categories may differ substantially between studies. Thus, in the Baris et al, 2001 study, a low cumulative number of runs in Philadelphia was defined as ≤ 3323, whereas Tornling et al., 1994, the highest cumulative run category in Stockholm was > 1000. These are very different exposure experiences, yet the mean duration of employment in the Philadelphia study was 18 years, while 61% of firemen in the Stockholm study continued until retirement, 69% of the total having begun employment before the age of 25 years (mean duration of employment not given). This comparison also highlights the difficulty in using employment time as a surrogate for exposure.

c. Data presentation

Other important characteristics of the studies reviewed are the weaknesses of proportionate mortality studies. As recognised and listed by Burnett et al. (1994) these include: the information on the death certificate may be inaccurate, especially for an occupational group that routinely retires early and may pursue other jobs; there is no information on possible confounders such as tobacco smoking and alcohol consumption; and there is no information on length of employment or possible occupational exposures. Proportional measures can be misleading because their denominator is the total number of cases or deaths from all causes, not only that being studied. Furthermore, the PMR method of estimating risk will overestimate risk if the overall death rate for the occupational group is low, as might be the case for firemen (DeCouflé et al., 1980). If this assumption is correct, then these reservations would apply to the studies of Grimes et al. (1991) and Burnett et al. (1994) in which data were reported as PMRs. To obtain the Mortality Odds Ratios (MOR) used by Ma et al. (1998), the expected numbers were calculated using all causes of death except cancers from the same occupational mortality database from which the firemen's deaths were obtained. As noted for PMRs, this measure relies on death certificate information and is therefore prone to bias because of misclassification of both the cause of death and the exposure.

2. Criteria for causation

The database consisting of the reviewed studies was interpreted according to widely agreed criteria of causation. These are:

1. Consistency of the observed association;
2. Strength of association
3. Temporal sequence of events;
4. Dose-response relationship;
5. Specificity of the association;
6. Biological plausibility of the observed association;
7. Experimental evidence.

A consistent effect must be seen in several studies in different populations and at different times; no single study can provide definitive evidence for a relationship. The strength of the association (the size of the relative risk) is also important for inference of causality, as is the correct time sequence of exposure and response, and dose-response relationship. Furthermore, the effect should show a specificity following a particular exposure and be biologically plausible.

Expressions of relative risk of urinary bladder were increased in seven of the 16 studies:
Vena & Fiedler (1987), SMR 2.86 (CI 1.30-5.40);
Sama et al. (1990), SMORp 2.11 (CI 1.07-4.14), SMORm 1.59 (CI 1.02-2.50);
Guidotti (1993), SMR 3.16 (CI 0.86-8.08);
Aronson et al. (1994) SMR 1.28 (0.51-2.63);
Demers et al. (1994) $SIR_{(police)}$ 1.7 (CI 0.7-4.3), $SIR_{(men, general)}$ 1.2 (CI 0.7-1.9);
Ma et al. (1998) $MOR_{(white\ men)}$ 1.2 (CI 0.9-1.6);
Baris et al. (2001) SMR 1.25 (CI 0.77-2.00).

In addition, increases in risk for urogenital or urinary tract cancers (which may or may not include urinary bladder) were observed in two studies:
Grimes et al. (1991), PMR 2.28 (CI 1.28-4.06);
Deschamps et al. (1995) SMR 3.29 (CI 0.40-11.88).

Of the remaining seven studies, five had risk ratios close to unity and only two had risk ratios substantially lower than unity:
Beaumont et al. (1991) SMR 0.57 (0.19-1.35) and
Demers et al. (1992) IDR 0.16 (CI 0.02-1.24), SMR 0.23 (CI 0.03-0.83).
Both of the latter relied on death certificate information, a source that Demers et al. (1994) later believed to be inferior to tumour registry data.

Overall, there is reasonable directional consistency in the data, although the effects observed were not large. An important point to consider is that, generally, the numbers of cases were small. The five largest numbers of urinary bladder cancer cases were in Ma et al. (1998) with 48 white men analysed as MOR = 1.2, Burnett et al. (1994) with 37 men analysed as PMR = 0.99, Sama et al. (1990) with 26 cases analysed as SMORp = 2.11 and SMORm = 1.59, Demers et al. (1994) with 18 cases analysed as SIRp = 1.7 and SIRm = 1.2, and Baris et al. (2001) with 17 males analysed as SMR = 1.25. The remaining numbers of cases in the individual studies were less than 10.

The associations that were observed were generally weak, although two of the SMR values were > 2 (Vena & Fiedler, 1987; Guidotti, 1993) and temporal considerations clearly showed that prolonged potential exposure preceded discovery of the disease.

A general problem affecting studies with firemen is that reliance by the investigators upon the number of years employed as a surrogate for actual exposures at fires has most probably resulted in misclassification. Consequently, number of years employed might not form a sound basis for describing dose-response relationships. Austin et al., 2001a provide such evidence, as only 66% of fire department personnel were in fact 1st line combat fire fighters and many of these combat firemen moved into non-exposed jobs before the end of their careers. In the same study there was a good correlation between the number of runs to fires and the time spent at fires, and they concluded that the number of runs would be a better surrogate for exposure than years worked as a fireman. However, it was also found that the number of runs may seriously over- or under-estimate the time spent at fires for individual crews, so that time spent at fires is the preferred surrogate. In one example, two crews had almost identical numbers of fire runs, but one spent 1.72 times longer at fires than the other. These results are contrary to the opinion of Guidotti & Goldsmith (2002) who specifically do not advise that job assignments or cumulative number of fire alarms to which firemen were assigned be used as measures of exposure (the only practical basis being, in their estimation, duration of employment). Within the studies reviewed here, Baris et al. (2001) used not only duration of employment, but also estimated cumulative number of runs and number of runs during the first 5 years as a fireman. The last estimate of exposure was divided into two groups, low and high and the relative risk was greater in the high number of runs category (Relative Risk 2.59). However, neither the cumulative number of runs (three categories) nor the duration of employment (three categories) showed a pattern of increasing risk with increasing surrogate measure of exposure. Thus, the evidence of an association coming from a dose-response relationship is weak. Year of first employment as a fireman, which was used in several of the studies, including Baris et al. (2001), is, in the opinion of this reviewer, more a measure of latency than exposure, since job categories are likely to have changed over the years.

Given the independently accumulated evidence that PAHs are probably a risk for urinary bladder cancer (see Urinary Bladder Tumours, above) and the certain exposure of firemen to PAHs in their work, there is a biological plausibility to the suggestion that urinary bladder cancer can be a result of exposures encountered in this occupation. Experimental carcinogenicity studies have clearly and repeatedly demonstrated the carcinogenicity of mixtures of PAHs as well as individual representatives of the chemical class (reviewed and summarised in WHO, 1998). However, tumour induction (usually in rats and mice) has been demonstrated on skin, in the respiratory system, the forestomach and small intestine, there being no outstanding evidence for the experimental induction of urinary bladder tumours by PAHs.

3. Latency

An important factor for consideration is latency, this being the time between first exposure to the supposed risk factor and clinical diagnosis. In many epidemiological studies, however, the longer time interval between first exposure and death is all that is available. A rule of thumb that is often adopted is that the latency for a solid tumour is about 20 years, with the understanding that there is a variation around this figure and that it can be shortened under the influence of a strong exposure. In

principle, more reliable estimates of latency can be derived from exposures that result in unequivocal increases in risk that have been confirmed in independent studies. Such exposures were encountered by dyestuffs workers and dye users before the banning from industrial use of 2-naphthylamine and benzidine, where relative risks > 10 have been frequently reported and have reached values of > 1000 in the most highly exposed populations (Meigs et al., 1986). In dyestuffs workers in Italy, the mean time from first exposure to death from bladder cancer was 25 years, with a range of 12 to 41 years (Decarli et al., 1985; Piolatto et al., 1991; Rubino et al., 1982). It was also observed that there was an inverse relationship between age at first exposure and the magnitude of the risk; those first employed before age 25 years having relative risk of 200. Furthermore, relative risk decreases with time since the lasat exposure.

In contrast, exposures in the Söderberg pot rooms in the Province of Québec aluminium industry have produced much lower relative risks, yet the latency appears to be no longer than that experienced in the dye industries. Thériault et al. (1984) found that relative risks according to duration of employment were 1.0 for < 1 year, 1.9 for 1 – 9 years, 3.0 for 10 – 19 years, 3.2 for 20 – 29 years and 4.5 for > 30 years, a trend that was statistically significant. A meta-analysis of systematically extracted results from 40 studies in foundry workers found a summary risk estimate for urinary bladder cancer of 1.11 (Gaertner & Thériault, 2002). These studies included three particularly large worker populations with good exposure information in which the data were broken down according duration of employment. One of these was a large cohort mortality study in Danish foundry workers in which it was found that employment for 20 or more years resulted in increased risk. Another was a case-control study of German foundry workers in which a raised risk occurred after 30 years employment. The third large study, an incidence study in Sweden, found no dose-response trend or increased bladder cancer risks among aluminium foundry workers.

A better reflection of the latency of a particular tumour type in particular exposure circumstances can probably come from epidemiological studies that are directly relevant. In the case of urinary bladder cancer amongst firemen, there are three potentially better sources of this information: the mortality studies of firemen in Buffalo, New York (Vena & Fiedler, 1987), Alberta (Guidotti, 1993) and Philadelphia, Pennsylvania (Baris et al., 2001). In none of these studies, however, was there any opportunity to control for tobacco use. Overall, smokers appear to have two-to-three times the risk of non-smokers (see Introduction), therefore, smoking is a potential confounder, particularly when the risks are low.

In both Buffalo and Alberta, the first indication of an increase in the SMR was observed in men who had worked at least 30 years. Maximum risk was observed > 50 years after entry to the service in Buffalo and 40-49 years after entry in Alberta. In Philadelphia, out of a total of 17 cases, 4 occurred after ≤ 9 years (SMR = 1.36, 95% CI 0.51 – 3.61); 7 occurred in the employment duration range 10 – 19 years (SMR = 1.48, 95% CI 0.70 – 3.09); and the remaining 6 cases occurred in the employment duration range ≥ 20 years of service (SMR = 1.01, 95% CI 0.45 – 2.25). Thus, no statistically significant increases in risk were found and although both the Vena & Fiedler (1987) and Guidotti (1993) studies suggests a latency of at least 30 years, this estimate is based upon very small numbers, and, furthermore, the Baris et al. (2001),

Philadelphia, study data on duration of employment could give no indication of latency because there is no significant indication that exposures incurred during employment as firemen were responsible for the bladder cancers in this population. Therefore, evidence from exposures to firemen would suggest latencies for bladder cancer of at least 30 years, a period that is similar to, or longer than, latencies suggested by studies of other exposures. This estimate is based on very small numbers of cases and time to diagnosis will, of course, be shorter.

4 Routes towards a conclusion.

The steps that are to be followed in arriving at a conclusion regarding the way that a particular disease should be handled by a compensation authority are:

1. hazard identification, based on an evaluation of the available studies;
2. judgment as to whether it is more likely than not that the exposure is the cause of the disease within that population;
3. consideration of the characteristics of a particular individual to see if that judgment can be applied without modification or whether it should be modified in either direction.

a. Nomenclature used by the International Agency for Research on Cancer

The strongest (*sufficient*, in IARC terms) evidence for a causal relationship is when a positive relationship has been established between the exposure and human cancer in studies (note the use of the plural) in which chance, bias and confounding have been ruled out with reasonable confidence. Weaker (*limited*, in IARC terms) evidence for a causal relationship is when a causal relationship is considered to be credible, but chance bias and confounding cannot be ruled out with reasonable confidence. The evidence is considered *inadequate* when there are no data or the available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association. These terms are used in the context of hazard identification, not risk assessment.

b. Aetiological fraction

An alternative method of arriving at a judgment of "more likely than not" to be due to occupational exposure that has been suggested is the use of the "aetiological fraction," this being the (Relative Risk – 1)/Relative Risk. If the relative risk (RR) is > 2.0 then the requirement for toxic torts is said to have been met (Muscat & Huncharek, 1989)[2]. This criterion has been used more recently in relation to firemen (Guidotti, 1995), but less stringent conditions have also been applied (Guidotti & Goldsmith, 2002, who also quote the Industrial Disease Standards Panel of the Ontario Workers'

[2] Questions that appear to be left unanswered are whether: (1) the RR itself should be > 2.0, while the magnitude of the 95% confidence interval is of no interest; (2) the RR should have a lower confidence interval that is > 1 and a higher interval that includes 2.0; (3) the RR itself should be > 2.0 and the lower confidence interval should be > 1; or (4) the RR should have a lower confidence interval > 2.0. In the opinion of this reviewer, (1) is too lax and (4) is too stringent, while both (2) and (3) are consistent with the conventional requirement for statistical significance. Which of these is chosen has presumably been determined in the courts.

Compensation Board, 1994). The latter two publications seem to have settled on a Standardised Mortality Ratio of 1.7.

Conclusion

It is credible that exposures encountered as a fireman increases the risk urinary bladder cancer. The evidence would be described in IARC terms as *limited,* because of the likelihood of exposure misclassification, the small numbers of cases and although the results from different studies appear to point in one direction, few of the studies reported results that reached statistical significance and these did not include the potentially most informative studies (Demers et al., 1994 and Baris et al., 2001). In terms of ascribing an aetiological fraction, Baris et al. (2001) does not find an SMR of 2.0, or even 1.7, as would sufficient according to some publications, and Demers et al. (1994) only find an SIR of 1.7 when policemen were the comparison group, the SIR when men in the same counties were the comparison group being 1.2. Therefore, it cannot be automatically assumed that a fireman with urinary bladder cancer contracted the disease as a result of his/her employment.

Application of these arbitrary indicators of causality to an individual from a process that studies populations cannot dispel the need for wisdom and judgment. Furthermore, additional factors may modify the particular situation. These include consideration of the fireman's exposure as defined by:

1. ideally, the length of time the individual spent at fires, or
2. the cumulative number of fire runs for that individual, or
3. the cumulative number of fire runs for the crew/unit/fire hall(s) in which the individual was employed, or
4. length and category of employment, this being the least suitable exposure surrogate.

These additional factors to be considered also include an individual's personal characteristics, since these may indicate that his risk is greater or smaller than that of the general population. Most important of these is tobacco smoking. The potential for confounding by smoking when considering causality in urinary bladder cancer that is must negate any claims made because of occupation as a fireman; a life-long non-smoker would have a stronger claim. Other factors that may cast doubts on a claim are usage in the past of analgesics containing phenacetin and a history of multiple infections of the urinary tract . Lack of exposure to either of these factors would strengthen a claim, as would be black rather than white.

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***Table 1. Summary characteristics and results of studies on the relation between occupational exposure as a fireman and cancer.**

Reference	Study base & type	Reference group	Numbers	Risk* (95% C.L. or significance level)	Adjustments & Comments
Musk, et al., 1978	Firemen in Boston, MA Cohort 1915-75	Massachusetts men	5655 firemen with 367 cancer deaths	Urogenital combined SMR = 0.92, n.s.	No dose-response analysis. Based on death certificates. 104561 person-years actively working, 38414 person-years retirees
Eliopulos et al., 1984	Firemen in Western Australia, 1939-78	Western Australia men	990 firemen with 30 cancer deaths	All cancers, SMR = 1.09 (0.74-1.56) Urogenital, SPMR = 1.08 (0.29-2.76)	No dose response analysis. Based on death certificates. 16876 person-years
Vena & Fiedler, 1987	Firemen in Buffalo, NY, 1950-1979	White USA men	102 cancer deaths	All cancers, SMR = 1.09 (0.89-1.32) Bladder, 9, SMR = 2.86 (1.30-5.40) **Duration of employment** < 10 years Bladder, 1, SMR = 5.00 10 – 19 years Bladder, 0 20 – 29 years Bladder, 1, SMR = 1.25 30 – 39 years Bladder, 3, SMR = 2.14 > 40 years Bladder, 4, SMR = 5.71	Gradiant in the SMR with years of service for all cancers, colon and urinary bladder. 32858 person-years
Sama et al., 1990	Firemen in Massachusetts, 1982-86	Massachusetts police (p); Massachusetts white men (m)	315 cancer deaths	All cancers not recorded. Bladder, 26, SMORp = 2.11 (1.07-4.14) SMORm = 1.59 (1.02-2.50)	Cancer registry data
Beaumont et al., 1991	Firemen in SanFrancisco, California, 1940-82.	White USA men	3066 firemen with 236 cancer deaths	All cancers, RR = 0.95 (0.84-1.08) Bladder, 5, RR = 0.57 (0.19-1.35)	Analysis of dose-response inconclusive. Number of person years not stated.
Grimes et al., 1991	Firemen in Honolulu, Hawaii, 1969-88.	Hawaii men	205 deaths, including 58 cancer deaths.	All cancers, PMR = 1.19 (0.96-1.49) Urogenital, PMR = 2.28 (1.28-4.06)	Proportionality study. Small numbers of individual cancers No analysis of dose-reponse
Demers et al., 1992	Firemen in Seattle, Tacoma WA & Portland, OR USA, 1945-89	Police in the same cities (p) White USA men (m)	4401 firemen with 291 cancer deaths	All cancers, 291, IDRp = 0.97 (0.67-1.33) S MRm = 0.91 (0.85-1.07) Bladder, 2, IDR = 0.16 (0.02-1.24) SMR = 0.23 (0.03-0.83)	122852 person-years for the 3 cities Death certificate data (compare with Demers et al., 1994)
Giles et al.,1993	Firemen in Melbourne,	Men in Victoria	2865 firemen,	All cancers, 50, SIR = 1.13 (0.84-1.48)	20853 person-years of observation

	Australia, 1980-89		50 cancer cases	Urinary tract, SIR = 1.02 (0.28-2.62)	Dose-response analysis non-significant
Guidotti, 1993	Firemen in Edmonton & Calgary, Alberta, 1927-87	Men in Alberta	3328 firemen with 92 cancer deaths	All cancers, 94, SMR = 1.27 (1.02-1.55) Bladder, 4, SMR = 3.16 (0.86-8.08)	Follow-up of 96% of the cohort for 64983 person-years. Weighting of years of service with job category time at fires estimates: fireman lieutenant, captain = 1; safety/training = 0.2; district chief = 0.1; desk job – 0.0. Dose-response analysis inconclusive
Aronson et al., 1994	Firemen in Toronto, Ontario, 1959-89	Men in Ontario	5414 firemen with 199 cancer deaths 7 bladder	All cancers, 199, SMR = 1.05 (0.91-1.20) Bladder, SMR = 1.28 (0.51-2.63)	114008 person-years of follow-up. Dose response analysis non-significant..
Burnett et al., 1994	Firemen in 27 states of the USA, 1984-90	Men who died in the same 27 states of USA	Number of firemen not stated. 1636 cancer deaths	All cancers, 1636,PMR = 1.10 (1.06-1.14) < 65 years age, 663, PMR = 1.12 (1.04-1.21) Bladder, 37, PMR = 0.99 (0.70-1.37) <65 years age, 9, PMR = 1.01 (0.46-1.93)	Proportionality study. Large number of cases, but no information on possible confounders, length of employment or occupational exposures.
Demers et al., 1994	Firemen in Seattle & Tacoma, WA USA, 1974-89.	Police in the same cities (p) Men in the same counties (m)	2447 firemen with 244 cancer deaths	All cancers, 224, SIRp = 1.0 (0.8-1.3) SIRm = 1.1 (0.9-1.2) Bladder, 18, SIRp = 1.7 (0.7-4.3) SIRm = 1.2 (0.7-1.9) **Duration of exposed employment** < 10 years Bladder, 4, SIR = 2.2 (0.6-5.6) 10 – 19 years Bladder, 2, SIR = 0.9 (0.1-4.6) 20 – 29 years Bladder, 9, SIR = 1.0 (0.4-1.8) ≥ 30 years Bladder, 3, SIR = 1.6 (0.3-4.8)	Tumour registry data (compare Demers et al., 1992)
Deschamps et al., 1995	Firemen in Paris, France, 1977-91	Men in the general population of France; age and cause-specific cancer rates	830 firemen with 18 cancer deaths	All cancers, 18, SMR = 0.89 (0.53-1.40) Genito-urinary, 2, SMR = 3.29 (0.40-11.88)	
Ma et al., 1998	Mortality odds ratio study of death certificates of firemen for race-specific	Men who died from causes other than cancer	6607 deaths of firemen with 1883	**WHITE**: All cancers, 1817, MOR = 1.1 (1.1-1.2) Bladder, 48, MOR = 1.2 (0.9-1.6)	Small numbers for some cancers in whites, small numbers for most cancers in blacks, leading to instability of the MORs

	cancer risk in 24 states of USA, 1984-93		cancer deaths (1817 white, 66 black)	**BLACK** All cancers, 66, MOR = 1.2 (0.9-1.5) Bladder, 1, MOR = 1.3	Database similar to Burnett et al., 1994, but extended by 3 years and 3 states not included; similar strengths and weaknesses.
Bates et al., 2001	Historical cohort study of all firemen in New Zealand, 1977-95	Men who died from cancer in the same period throughout New Zealand	4221 firemen	All cancers, 118, SIR = 0.95 (0.8-1.1) Bladder, 5, SIR = 1.14 (0.4-2.7)	58709 person-years. Data do not include 2/4 testicular cancer cases occurring in the Wellington cluster (Bates & Lane, 1995) Results (notably for testes) not changed by analysis for 1990-96 period (Cancer Registry database more complete from about 1990)
Baris et al., 2001	Historical cohort mortality study of Philadelphia firemen employed 1925-86	Men in the general USA population	7789 firemen with 2220 deaths	All cancers, 500, SMR = 1.10 (1.00-1.20) Bladder, 17, SMR = 1.25 (0.77-2.00) **Duration of employment:** ≤ 9 years Bladder, 4, SMR = 1.36 (0.51-3.61) 10 – 19 years Bladder, 7, SMR = 1.48 (0.70-3.09) ≥ 20 years Bladder, 6, SMR = 1.01 (0.45-2.25) **Year of hiring (1925-1986)** Before 1935 Bladder, 11, SMR = 1.71 (0.94-3.08) 1935-1944 Bladder, 5, SMR = 1.17 (0.49-2.81) After 1944 Bladder, 11, SMR = 0.35 (0.05-2.43) **Cumulative number of runs** Low (<3323 runs) Bladder, 4, SMR = 1.20 (0.44-3.18) Medium (≥3323 & <5099 runs) Bladder, 1, SMR = 0.50 (0.07-3.56) High (≥5099 runs) Bladder, 1, SMR = 0.54 (0.08-3.81) **Runs during first 5 years as fireman** Low (≤729 runs) All cancers, 171, RR = 1.00 Bladder, 2, RR = 1.00 High (>729 runs)	204821 person-years of follow-up. Thus, the largest study available to date. Reliance on death certificates for cause. Best estimates of exposure because, in addition to duration of employment, the cohort was analysed according to job assignment and – most importantly – number of runs.

				All cancers, 169, RR = 1.05 Bladder, 4, RR = 2.59 (0.46-14.59)	